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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,708	11/17/2000	Michael Tyo	08191-012001	8526

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 07/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/715,708	Applicant(s) Hedley
	Examiner Dave Nguyen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be availeble under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 2, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Nov 17, 2000* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4, 5, 6*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election without traverse of the species: residual organic solvent level of less than 200 ppm (claim 10), drying step for washed microparticles comprising lyophilizing (claim 13); removing organic solvent from a second emulsion by extraction (claim 22); diameter of microparticles less than 20 um (claim 33); ratio of lactic acid to glycolic acid in the PLGA is about 1:1 by weight (claim 38); and average residence time of the first emulsion and the second aqueous solution in the mixing chamber is less than about 60 seconds (claim 44), in the response filed May 2, 2003 is acknowledged.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6, 20-26, 32, 33, 35-44 are rejected under 35 USC 102(e) as being anticipated by, or in the alternative, under 35 USC 103(a) as being unpatentable over Shah (US Pat No. 6,020,004).

Shah teaches continuous processes for the preparation of 0.5 micron microparticles for agene delivery, wherein the agent can be a nucleic acid, which processes of preparation comprises mixing in a homogenizer (mixing chamber) a fist emulsion comprising poly-lactic-co-glycolic acid at ratios between 1:2 and 4:1, w/w, with a first aqueous solution containing a biological agent including nucleic acids, further comprising mixing this solution with a second aqueous solution which comprises a surfactant, a stabilizer including sucrose, a lipid and a buffer, and further mixing this combination to form a second emulsion further comprising poly-vinyl-alcohol, then removing by lyophilization following the addition of an excipient, or alternatively, by evaporation or extraction (column 1, line 41-51-column 2, line 46; column 4, lines 24-65; column 5, line 52-column 7, line 50; Example 1-8, column 8, line 18-column 11, line 19, including tables 2 and 3).

To the extent that Shah does not teach minor modification including any particular ratio that falls within the ratio of 1:2 and 4:1 (PLGA, w/w), the step of adding a homogenizing agent to ensure a thorough mixing any of the emulsions in the homogenizer, and the use of any mixing device/solvent removal device known in the art of polymer, it would have been obvious to one of ordinary skill the art that the minor modifications are matters of design choice and within the level of one ordinary skill in the art of polymer chemistry.

Thus, the claimed invention is anticipatory, or in the alternative, is *prima facie* obvious.

Claims 1-47 are rejected under 35 USC 103(a) as being unpatentable over Shah as applied to claims -3, 6, 20-26, 32, 33, 35-44 above, taken with Cleland (US 5,643,605), and further in view of Hilfinger (US 6,048,551).

The claims are drawn to a process of making microparticles comprising continuously supplying a first emulsion comprising PLGA and an organic solvent such as methylene chloride, which solution is mixed with an aqueous solution comprising nucleic acid, and further continuously supplying a second aqueous solution comprising a surfactant to be mixed with the first emulsion, wherein this resulting second emulsion further comprises a stabilizer, such as a

carbohydrate and a buffer (i.e., TRIS-EDTA) and further comprising a lipid, wherein waste solutions are removed following mixing and the resulting microparticles are concentrated and washed by a diafiltration apparatus, and further treated by evaporation, extraction and/or lyophilization.

Shah is relied upon as cited in the 102 rejection above,

Shah does not teach the use of a diafiltration apparatus or a fine mesh screen for washing and concentrating microparticles as additional steps prior lyophilization. Shah does not teach the use of EDTA as part of the stabilizing solution in making the microparticles.

Cleland teaches processes of making microparticles comprising continuously supplying a first emulsion comprising PLGA (ranging from 100:00 to 00:100, wt polylactic acid:wt polyglycolic acid), wherein the PLGA has an average molecular weight between 6,000 and 10,000 daltons, and which first emulsion comprises an organic solvent such as methylene chloride, which solution is mixed with an aqueous solution comprising a nucleic acid, and further continuously supplying a second aqueous solution a surfactant such as Tween to be mixed with the first emulsion, wherein this resulting second emulsion further comprises a stabilizer, such as sucrose and a buffer (i.e. TRIS-EDTA), wherein the second emulsion is mixed in a fermenter and such mixing occurs between 2°C and 8°C, whereby the resulting microparticles are concentrated and washed, and waste aqueous and organic solvents are removed by a combination of filtering using a diafiltration apparatus, organic solvents are extracted, lyophilized and evaporated (column 3, line 18-column 4, line 65; column 9, line8-column 9, line 58; column 13, lines 20-37), whereby the organic solvent remaining is less than 50 ppm. In addition, the size of the microparticles was taught by Cleland to be a function of emulsion viscosity, impeller speed, polymer concentration and polymer molecular weight, so that particle size is adjusted as desired (column 21, lines 1-40, also see table 1).

Hilfinger teaches microsphere encapsulation of gene transfer vectors using biologically degradable polymers comprising PLGA, whereby the microparticles are filtered on 0.2 um filters and whereby functional recombinant viral vectors further comprising a heterologous insert was successfully deliver and functionally expressed in a target cell in vivo (column 11, line 44-column 12, line 17; column 14, line 51, column 16, line 21).

It would have been obvious to one of ordinary skill in the art to devise a process for the synthesis of microparticles for nucleic acid delivery comprising a continuous flow, double emulsion method because such methods had been taught in the prior art for the delivery of

various biological effectors, including nucleic acids as taught by Hilfinger and Cleland. One of ordinary skill in the art would have been motivated to synthesize microparticles comprising the continuous mixing of a first emulsion comprising PLGA in an organic solvent with an aqueous solution comprising the agent to be delivered because it had been taught previously by Shat and the references cited therein that polymers of PLGA function to encapsulate molecules for delivery *in vivo*, and many variations of making microparticles comprising these polymers have been reported as a routine matter in the art (See the cited references, particularly Shah on column 1, lines 51-51), wherein such processes include a double emulsion, continuous flow technique as taught by Shah, and whereby the microparticles are washed and concentrated using such techniques as filtering, lyophilizing, evaporating and extracting, as taught by Cleland, and whereby the aqueous solutions used in the process comprise stabilizing agents, surfactants, lipids, bioactive materials including nucleic acids, chelating agents such as EDTA, and a variety of buffers known in the prior art, depending on the bioactive agent to be deliver and the desire size of the finalized microparticles produced by the process taught by the combined cited references. One of ordinary skill in the art would have expected that the process for making microparticles as taught by the combined cited references yields microparticles in the range of 0.5 to 2.5 microns, and that particle size is adjusted by altering mixing conditions, polymer concentration and polymer molecular weight. Furthermore, one of ordinary skill in the art would have expected that either supercoiled DNA or circular RNA molecules are included within the nucleic acid component of the microparticles, because the conditions for encapsulating nucleic acids within microparticles without destroying their structure, thereby allowing for the for the intracellular delivery of functional DNA or RNA using microparticles, was a routine matter at the time the invention was made. Furthermore, one of ordinary skill in the art would have been motivated to optimize steps involved in the process of microparticle synthesis including washing, mixing, concentration and sterilization steps, and one of ordinary skill in the art would have expected that the alterations of such steps would have been a routine matter, since all of the components included the steps were known in the prior art, the concept of employing double emulsions in mixing chamber, deafiltration apparatus and/or solvent removal devices extraction/lyophilization steps in the art of making polymeric microparticles were taught by the combined cited references, particularly since their successful use and the implementation of double emulsion, continuous flow synthetic techniques for the synthesis of microparticles for the

making of microparticles composed of PLGA entrapping nucleic acids of choice had been taught in the totality of the prior art of record.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-47 are rejected under 35 USC 103(a) as being unpatentable over Shah as applied to claims -3, 6, 20-26, 32, 33, 35-44 above, taken with Cleland (US 5,643,605), and Hilfinger (US 6,048,551), and further in view of Hartounian (US 2002/0039596), Dutton (US 4,957,708), applicant's admission over the availability of deafiltration apparatuses on page 20.

To the extent that the claims embrace the use of known mixing chambers and/or diafiltration apparatuses, and/or solvent removal devices for production of microparticles in large quantities and/or at a commercial scale, Hartounian, Dutton, and page 20 of the as-filed specification are further exemplified to indicate that these mixing chambers, deafiltration devices are well known in the prior art of producing particles by emulsion techniques.

As such, and to the extent that the rejection of all pending claimed by the combined Shah, Cleland and Hilfinger is applied here as indicated above, it would have been obvious for one of ordinary skill in the art to optimize the production process by employing any known mixing chambers and/or deafiltration apparatuses, and/or solvent removal devices in the microparticle production process as taught by the combined Shah, Cleland and Hilfinger references. One of ordinary skill in the art would have been motivated to do so in order to enhance the production of large quantities of microparticles for use in the delivery of nucleic acids and to reduce the time in preparing the desire amount of microparticles. Since the totality of the prior art of record teaches that the microparticles are for use in an *in vivo* environment, one of ordinary skill in the art would have been motivated to ensure that all of the equipments and/or components used in the making of the microparticles are sterile, so as to ensure that sterility is preserved throughout the process, also see page 5 of Hartounian for the importance of having sterility preserved during a process of making particle carriers for biologically active agents..

Thus, the claimed invention as a whole, was *prima facie* obvious.

The following prior art are additionally cited to indicate that the state of the prior art the making of polymeric microparticles which encapsulate supercoiled DNA and/or intact plasmid

vectors is well established, and that techniques of employing double emulsions, and/or solvent extraction/liophilization are also well-established: Hedley (WO 98/31398), Hedley II, US 5,783,567, Ando, US 6,197,229, Mathiowitz US 6,475,779, and Mathiowitz II, US 6,248,720.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051**.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER